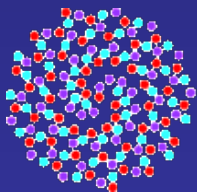


# In Pursuit of a Working Model...

## ... The Curation Process

Catherine Lloyd



MAURICE WILKINS CENTRE  
FOR MOLECULAR BIODISCOVERY



# Talk Outline

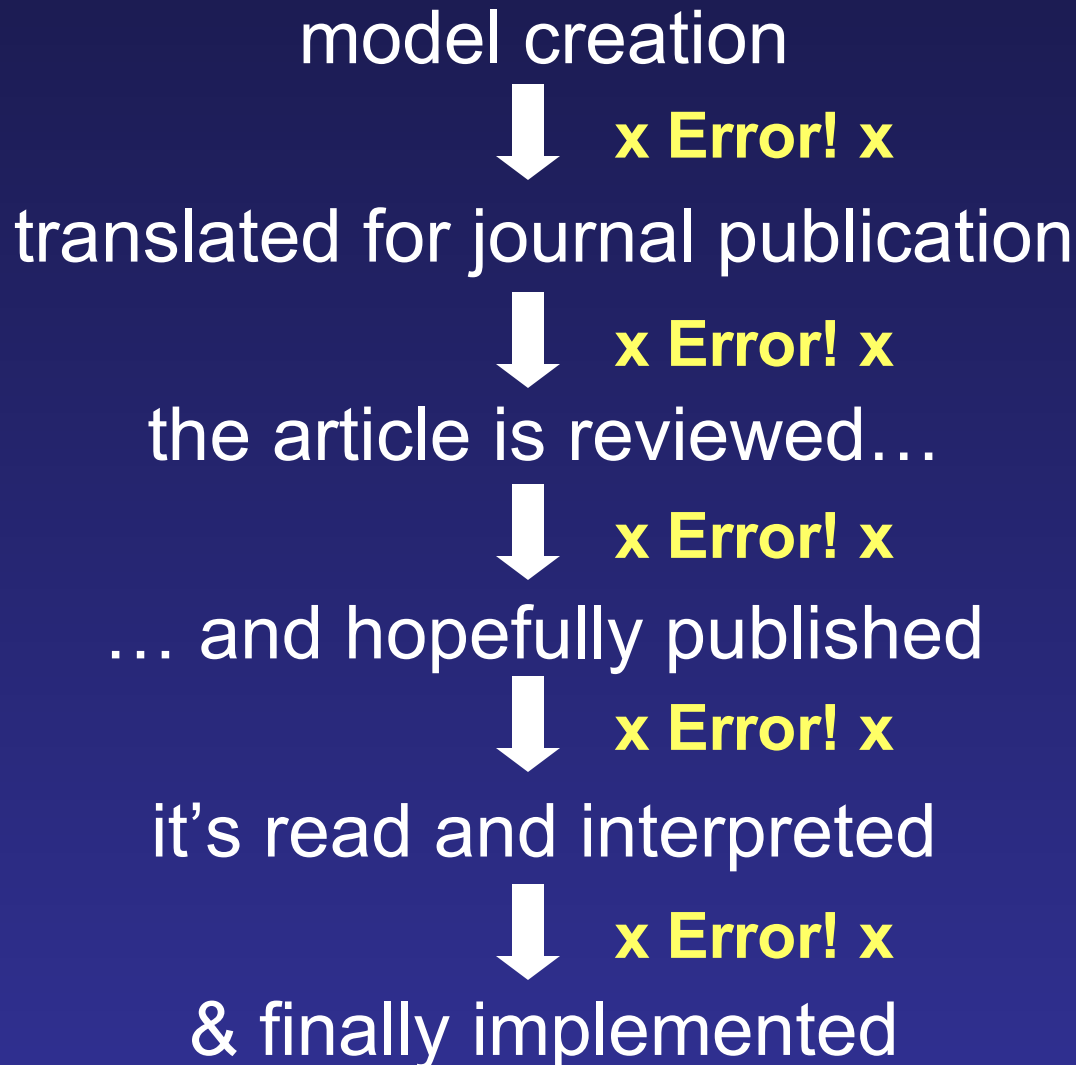
The problems with publishing

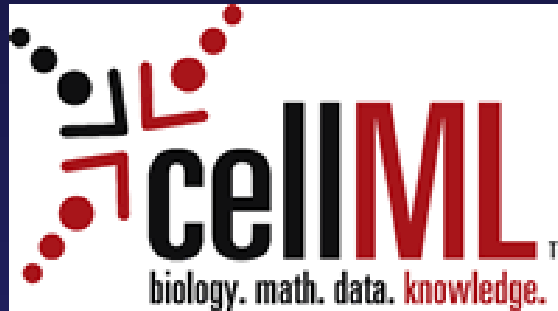
CellML as a solution

Creating and curating CellML models

Future goals

# The Publishing Process..





CellML has evolved as a potential solution to the inconsistencies between computational and published models

It's an XML-based markup language which can be used to describe biological models

It's flexible structured to encourage model exchange, reuse and further development

# Original Code → Published Paper → CellML

```
%-----Calc the L-type Ca
current-----

[CfCa,RevPCa]=
CalcConstantfield(Cai,Cao,2, Vm); %Ca
[CfK,RevPK] =
CalcConstantfield(Ki,Ko,1, Vm); %K
[CfNa,RevPNa] =
CalcConstantfield(Nai,Nao,1, Vm); %Na
if (count ==1 && currenttime == 0)
    Va = -74.0078;
else
    Va = Vm;
end
if (count ==0)
    [mcal, hcal,n] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
ICaLK = (0.001 * PCAL *
CfK)*mcal*hcal;
%ICaLCa = (PCAL * CfCa*mcal*hcal)
%original
ICaLCa = (PCAL * CfCa*mcal*hcal);
ICaL = ICaLCa + ICaLK+ICaLNa;
else
    ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
ICaLK = (0.001 * PCAL *
CfK)*mcal*hcal;
ICaLCa = (PCAL * CfCa*mcal*hcal);
ICaL = ICaLCa + ICaLK+ICaLNa;
[mcal, hcal] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
end
```

The cell membrane is modeled as a capacitor connected in parallel with variable resistances and batteries representing the different ionic currents and pumps. The electrophysiological behavior of a single cell can hence be described with the following differential equation (23)

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m} \quad (1)$$

where  $V$  is voltage,  $t$  is time,  $I_{ion}$  is the sum of all transmembrane ionic currents,  $I_{stim}$  is the externally applied stimulus current, and  $C_m$  is cell capacitance per unit surface area.

Similarly, ignoring the discrete character of microscopic cardiac cell structure, a 2D sheet of cardiac cells can be modeled as a continuous system with the following partial differential equation (23)

$$\frac{\partial V}{\partial t} = -\frac{I_{ion} + I_{stim}}{C_m} + \frac{1}{\rho_x S_x C_m} \frac{\partial^2 V}{\partial x^2} + \frac{1}{\rho_y S_y C_m} \frac{\partial^2 V}{\partial y^2} \quad (2)$$

where  $\rho_x$  and  $\rho_y$  are the cellular resistivity in the  $x$  and  $y$  directions,  $S_x$  and  $S_y$  are the surface-to-volume ratio in the  $x$  and  $y$  directions, and  $I_{ion}$  is the sum of all transmembrane ionic currents given by the following equation

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{K2} + I_{K3} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bK} \quad (3)$$

where  $I_{NaCa}$  is  $Na^+/Ca^{2+}$  exchanger current,  $I_{NaK}$  is  $Na^+/K^+$  pump current,  $I_{pCa}$  and  $I_{pK}$  are plateau  $Ca^{2+}$  and  $K^+$  currents, and  $I_{bCa}$  and  $I_{bK}$  are background  $Ca^{2+}$  and  $K^+$  currents.

```
<component name="membrane">
  <variable units="millivolt" public_interface="out" cmeta:id="membrane_V"
name="V" initial_value="-86.2" />
  <variable units="joule_per_mole_kelvin" public_interface="out" name="R"
initial_value="8314.472" />
  <variable units="kelvin" public_interface="out" name="T" initial_value="310" />
  <variable units="coulomb_per_millimole" public_interface="out" name="F"
initial_value="96485.3415" />
  <variable units="microF" public_interface="out" name="Cm"
initial_value="0.185" />
  <variable units="micrometre3" public_interface="out" name="V_c"
initial_value="0.016404" />
```

```
<variable units="millisecond" public_interface="in" name="time" />
<variable units="picoA_per_picoF" public_interface="in" name="i_K1" />
<variable units="picoA_per_picoF" public_interface="in" name="i_to" />
<variable units="picoA_per_picoF" public_interface="in" name="i_Kr" />
<variable units="picoA_per_picoF" public_interface="in" name="i_Ks" />
<variable units="picoA_per_picoF" public_interface="in" name="i_NaK" />
<variable units="picoA_per_picoF" public_interface="in" name="i_Na" />
<variable units="picoA_per_picoF" public_interface="in" name="i_b_Na" />
<variable units="picoA_per_picoF" public_interface="in" name="i_NaCa" />
<variable units="picoA_per_picoF" public_interface="in" name="i_b_Ca" />
<variable units="picoA_per_picoF" public_interface="in" name="i_p_K" />
<variable units="picoA_per_picoF" public_interface="in" name="i_p_Ca" />
<variable units="picoA_per_picoF" public_interface="in" name="i_Stim" />
```

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci>time</ci></bvar>
      <ci>V</ci>
    </apply>
    <apply><times />
      <apply><divide />
        <apply><minus />
          <cn cellml:units="dimensionless">1</cn>
          <apply>
            <cn cellml:units="dimensionless">1</cn>
          </apply>
        </apply>
        <apply><plus /><ci>i_K1</ci>
          <ci>i_to</ci><ci>i_Kr</ci>
          <ci>i_Ks</ci><ci>i_CaL</ci>
          <ci>i_NaK</ci><ci>i_Na</ci>
          <ci>i_b_Na</ci><ci>i_NaCa</ci>
          <ci>i_b_Ca</ci><ci>i_p_K</ci>
          <ci>i_p_Ca</ci><ci>i_Stim</ci>
        </apply>
      </apply>
    </apply>
  </math>
</component>
```

# The Model Repository [www.cellml.org/models](http://www.cellml.org/models)

The CellML model repository began life as a set of examples to illustrate how the language could be applied and to test its features as it evolved

It later became a repository of previously published biological models, which were encoded in CellML based on the literature

The screenshot shows the CellML Model Repository website in a Firefox browser window. The address bar displays <http://www.cellml.org/models>. The page title is "CellML Model Repository".

**Left Sidebar:**

- Getting Started**
  - Overview
  - Terms Of Use
  - Scope
  - Specifications
  - Current Development
  - Road map
  - Project Team
  - Publications
  - FAQ
  - Related Efforts
- Use**
  - Repository
  - Tools
  - Downloads
  - Tutorial
    - Notation
    - XML Guide
    - Electrophysiological
    - Signal Transduction
    - CellML 1.1
    - Best Practice
- Community**
  - News
  - CellML Workshop
  - Wiki
  - Mailing Lists
  - Meeting Minutes
  - Contact Us
- Funding agencies**
  - wellcome trust
  - MRC CENTRE FOR CELLULOSE RESEARCH
  - aneurist
  - New Zealand Institute of Mathematics & its Applications

**Main Content Area:**

### CellML Model Repository

The models in the repository are in the process of being curated; those appended with a yellow star in the listing below indicates the model is correct according to the [curation guidelines](#).

**Actions:**

Submit a new model to the repository

**Full Text Search:**   [Advanced](#)

**Filter:**

**Model Type** --- All --- **Curation Level** --- All ---

### Repository Models

There are currently **312** unique models in the repository.

- ★ 2006 [The International System of Units \(SI\) 8th Edition, 2006](#)
- ★ 2006 [The International System of Units \(SI\) 8th Edition, 2006](#)
- ★ 2006 [The International System of Units \(SI\) 8th Edition, 2006](#)
- ★ 2002 [Dynamical description of sinoatrial node pacemaking: improved mathematical model for primary pacemaker cell](#)
- ★ Adrian, Chandler, Hodgkin, 1970 [Voltage clamp experiments in striated muscle fibres](#)
- ★ Albrecht, Colegrove, Friel, 2002 [Differential Regulation of ER Ca<sup>2+</sup> Uptake and Release Rates Accounts for Multiple Modes of Ca<sup>2+</sup>-induced Ca<sup>2+</sup> Release](#)
- ★ Albrecht, Colegrove, Hongpaisan, Pivovarov, Andrews, Friel, 2001 [Multiple Modes of Calcium-induced Calcium Release in Sympathetic Neurons I: Attenuation of Endoplasmic Reticulum Ca<sup>2+</sup> Accumulation at Low \[Ca<sup>2+</sup>\]<sub>i</sub> during Weak Depolarisation](#)
- ★ Aon, Cortassa, 2002 [Coherent and robust modulation of a metabolic network by cytoskeletal organization and dynamics](#)
- Asthagiri, Lauffenburger, 2001 [A Computational Study of Feedback Effects on Signal Dynamics in a Mitogen-Activated Protein Kinase \(MAPK\) Pathway Model](#)
- ★ Bakker, Mensonides, Teusink, van Hoek, Michels, Westerhoff, 2000 [Compartmentation protects trypanosomes from the dangerous design of glycolysis](#)
- Bakker, Michels, Oppendoes, Westerhoff, 1997 [Glycolysis in Bloodstream Form Trypanosoma brucei Can Be Understood in Terms of the Kinetics of the Glycolytic Enzymes](#)
- ★ Baylor, Hollingworth, Chandler, 2002 [Comparison of Simulated and Measured Calcium Sparks in Intact Skeletal Muscle Fibers of the Frog](#)
- ★ Beard, 2005 [A Biophysical Model of the Mitochondrial Respiratory System and Oxidative Phosphorylation](#)

**Right Sidebar:**

**repository actions**

- [Browse Models](#)
- [Search](#)

**Quicklinks:**

- [Repository Home](#)
- [Newsfeed for New Models](#)
- [Previous Repository](#)

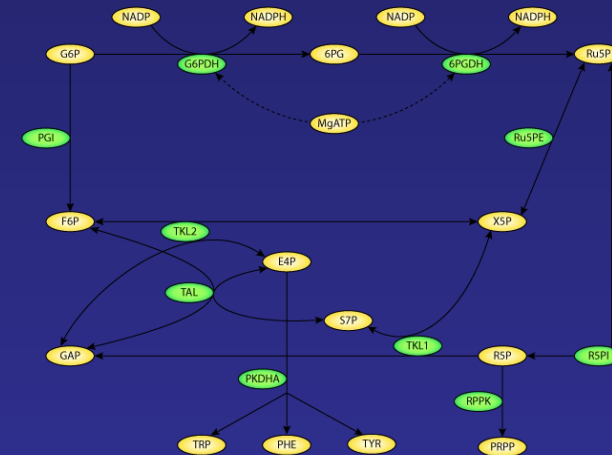
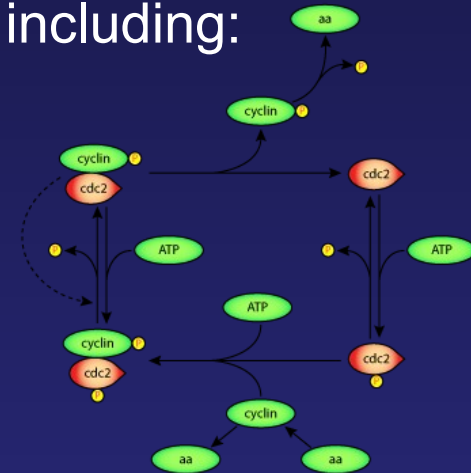
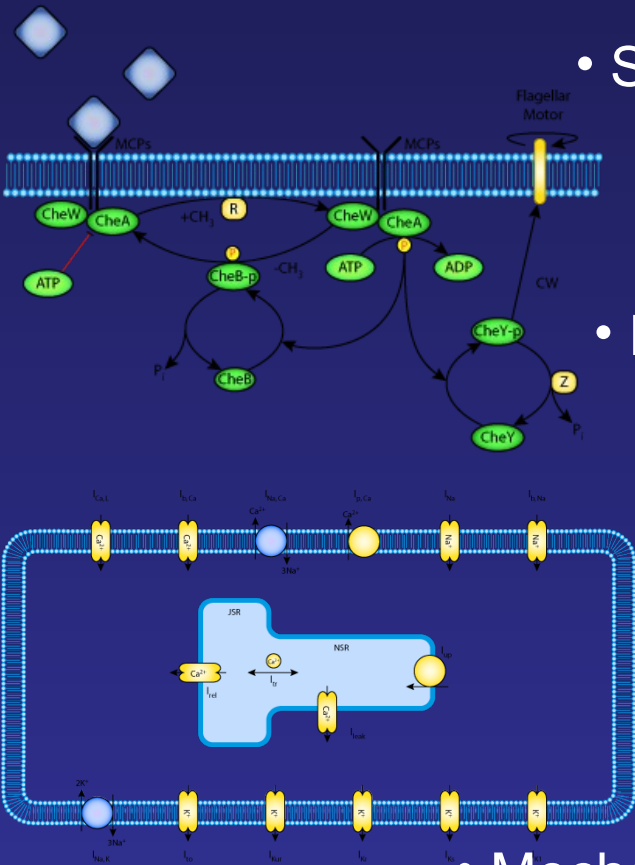
The browser window shows the system clock as Fri Mar 21, 3:47 PM.

# The Model Repository

[www.cellml.org/models](http://www.cellml.org/models)

There are now >300 models in the repository including:

- Signal transduction pathways
- Metabolic pathways
- Electrophysiological models
- Immunological models
- Cell cycle models
- Muscle models
- Mechanical models & Constitutive laws



# Model Creation & Curation

Initially, CellML models were written by hand in a text editor, and there was no way to test the models for consistency or completeness - they were simply checked by eye to see if they accurately represented the published model.

Since then tools, such as PCEnv and COR, have been developed to write and run CellML models, and these can also be used to curate the models in the repository.



# Model Curation: The Theory

Of the 300 models in the repository  $\sim 1/2$  have been curated

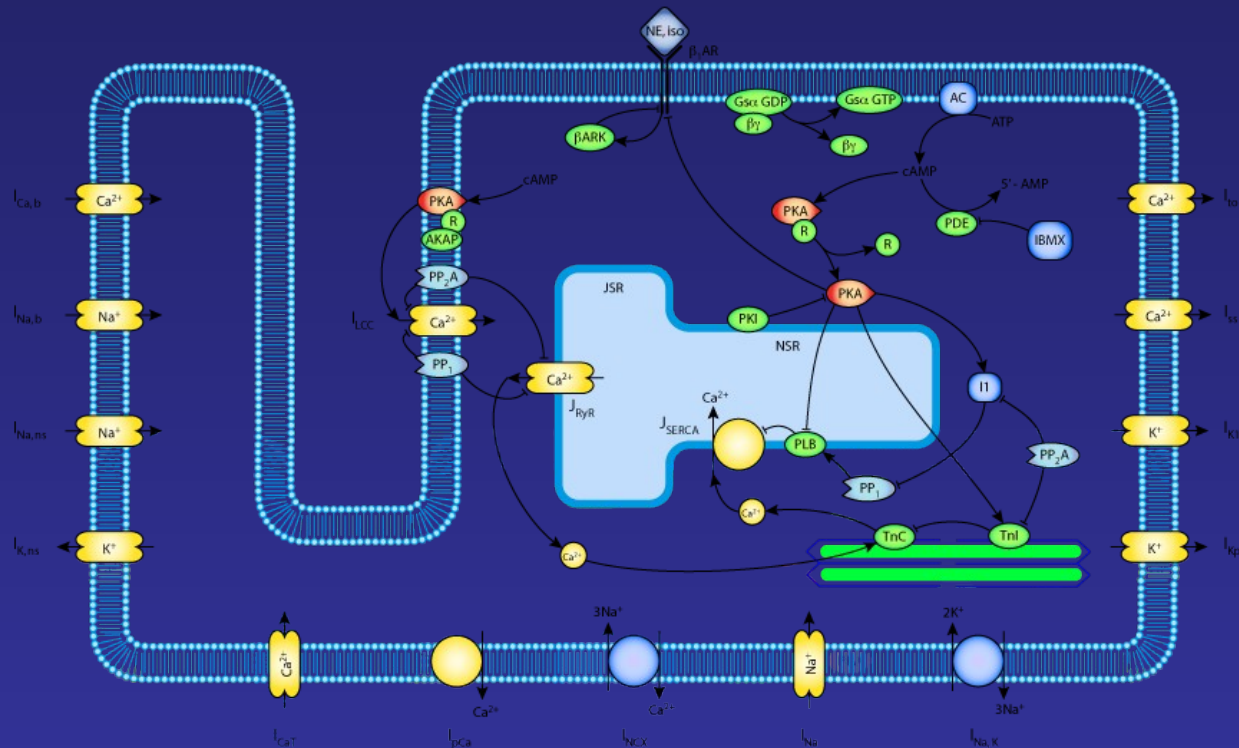
Curation Status: ★★☆☆	<a href="#">PCEnv</a> ★★☆☆ <a href="#">JSim</a> ★★☆☆ <a href="#">COR</a> ★★☆☆

- Level 0: Not curated
- Level 1: Consistent with the published paper
- Level 2: Checked for (i) typos, (ii) unit consistency, (iii) completeness, (iv) not over-constrained, and (v) the model reproduces the published results;
- Level 3: the model is checked for the extent to which it satisfies physical constraints such as conservation of mass, momentum, charge, etc. (conducted by domain experts)

# Point to Note

Model curation does not always imply “fixing” a model. A model may be valid CellML, and a true representation of the published paper, but there can be other reasons why the a CellML model won't run

e.g. Saucerman *et al.* 2003 includes coupled, non-linear equations.  
The CellML model is valid, but currently the simulation tools PCEnv and COR are unable to handle this type of equation.



# Model Curation – The Practice

1) The CellML models are run in PCEnv and COR  
& any obvious typos and unit inconsistencies are fixed

The screenshot shows the COR 0.9 [Editorial Mode] window. The top pane displays a complex MathML equation for the sodium current,  $i_{NaCa}$ . The equation is:

$$i_{NaCa} = \frac{I_{NaCa_{max}} \cdot \left( e^{\frac{0.35 \cdot F \cdot V}{R \cdot T}} \cdot Na_i^3 \cdot Ca_o - e^{\frac{-0.65 \cdot F \cdot V}{R \cdot T}} \cdot Na_o^3 \cdot Ca_i \right)}{\left( K_{mNa}^3 + Na_o^3 \right) \cdot \left( K_{mCa} + Ca_o \right) \cdot \left( 1 + K_{sat} \cdot e^{\frac{-0.65 \cdot V \cdot F}{R \cdot T}} \right)}$$

The bottom pane shows the corresponding CellML code with variables and their units:

```
var i_NaCa: pA_per_picoF {pub: out};
var I_NaCa_max: pA_per_picoF {init: 1600};
var K_mNa: millimolar {init: 87.5};
var K_mCa: millimolar {init: 1.38};
var K_sat: dimensionless {init: 0.1};
var time: millisecond {pub: in};
var V: millivolt {pub: in};
var R: joule_per_mole_kelvin {pub: in};
var T: kelvin {pub: in};
var F: coulomb_per_millimole {pub: in};
var Na_i: millimolar {pub: in};
var Na_o: millimolar {pub: in};
var Ca_i: millimolar {pub: in};
var Ca_o: millimolar {pub: in};

i_NaCa = I_NaCa_max * (exp(0.35 {dimensionless} * F * V / (R * T)) * pow(Na_i, 3 {dimensionless}) * Ca_o - exp(-0.65 {dimensionless} * F * V / (R * T)) * pow(Na_o, 3 {dimensionless}) * Ca_i) / ((K_mNa^3 + Na_o^3) * (K_mCa + Ca_o) * (1 + K_sat * exp(-0.65 {dimensionless} * V * F / (R * T))))

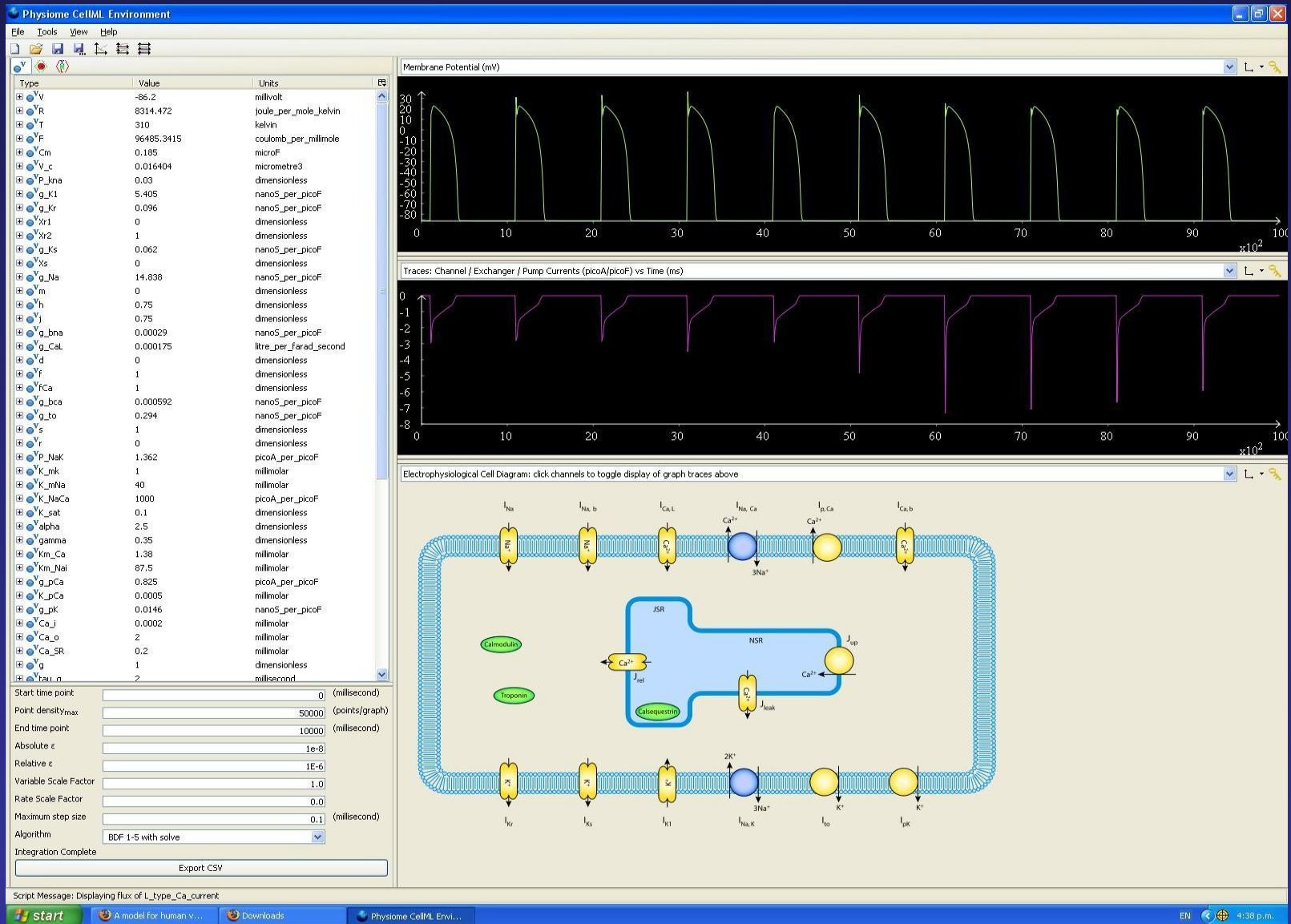
def comp background_currents as
var i_B_Na: pA_per_picoF {pub: out};
var i_B_Ca: pA_per_picoF {pub: out};
var g_B_Na: nanoS_per_picoF {init: 0.000674};
var g_B_Ca: nanoS_per_picoF {init: 0.00113};
var E_Ca: millivolt;
var E_K: millivolt {pub: in};
var F_Na: millivolt {pub: in};
```

The status bar at the bottom displays warning messages:

```
[Warning] ... \Users\clo007\Desktop\ramirez_nattel_courtemanche_2000_version02.celml (88): there is one or several problems with the units used in this equation
[Warning] ... \Users\clo007\Desktop\ramirez_nattel_courtemanche_2000_version02.celml (119): there is one or several problems with the units used in this equation
```

COR provides error messages & renders the MathML as readable equations

## 2) The simulation output is compared with the results in the published paper



### 3) Expert help is sought!

The model author is contacted and requests are made for missing parameters & equations, for general clarification and, where possible, the original code is retrieved

... often highlighting how error prone the publishing process is

**The value of 'a' was indeed missing**, it is 2.5218 (at temp = 286K). Also note that the value of delta-H for gamma should be 200240 rather than 200.24, this is an error in the Table (the period should have been a comma).

your guess is right:  $k_o$  and  $k_{-o}$  are 95 and 22/s, resp. They are not a function of voltage (as  $k_v$  and  $k_{-v}$ ). **I'll fix the bug in the table and make it clearer for the print version.**

Thank you for your interest in our work and your careful reading of the paper.

**Eq. 7 was printed wrong. Whilst proofreading the article for publication we found several misprints but we missed this one** (hopefully the only one). You are right, the last two iron terms in Eq. 7 should be in the ferrous form as in the pathway diagram (Fig. 1). Also,  $k_8$  and  $k_{8\_}$  should have their units swapped over.

Communication with the model authors also frequently results in their positive feedback on our CellML efforts

**That's sounds wonderful**, I'm glad you were able to get the code to match the published results. I'm also glad to hear about the student interested in our 2007 model, **it's always nice to know that someone other than myself is interested in the models.**

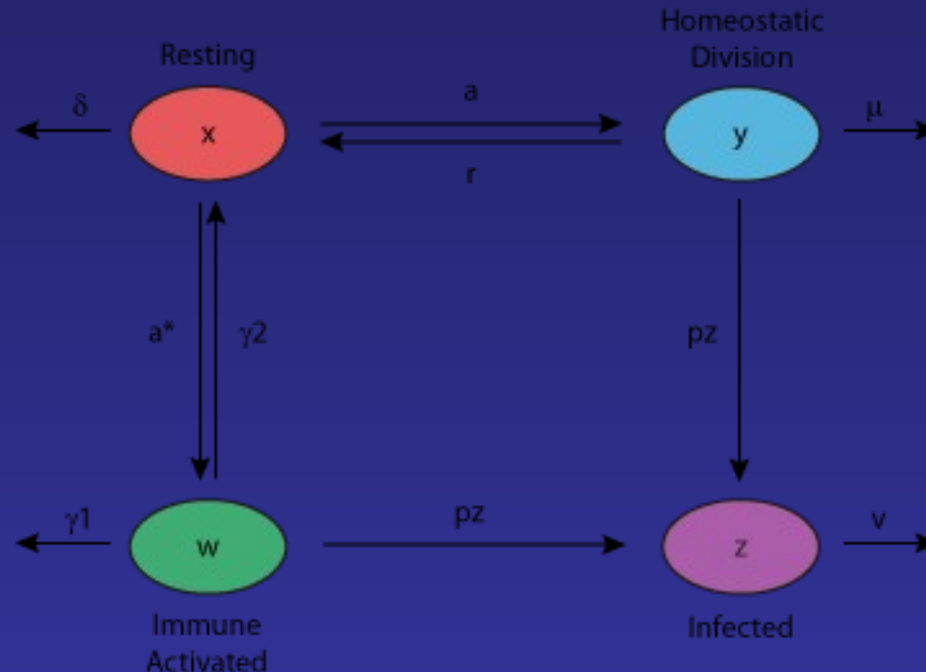
**I was glad to see that you chose to simulate our model** with your simulation set-up. I did not know about your system CellML. After my first look at it I thought it was an interesting tool, especially that it is coded in XML. **I will explore further the capabilities of your system more carefully...**

Parenthetically, I have been following the basic progress of some of the "ML" initiatives for the last few years, namely your effort and the SBML project. **I am delighted that you have chosen this model to use as an example in your repository. Quite exciting!**

**I am very flattered that you've chosen to put our models on your web site** (which I've just had a look at and it is great!).

# And, just occasionally, we become the “experts”!

I'm currently teaching Yates et al 2007's PLoS Med paper to a class of Zoology grad students and struggling mightily to replicate the authors' results. **The CellML model was extremely useful** in (1) identifying a typo in one of the equations in the published paper [the version on CellML agreed with common sense and the graphical model in the paper] and (2) identifying the scaling relation used to calculate one of the parameters ( $\mu$ ) from the values of the other parameters.





# Future Goals

To complete the curation of all the models in the repository... ideally such that they recreate the results in the published paper

To encourage model developers (and journals) to publish their models in CellML code concurrent with their written paper



# Acknowledgements

Curation Team: James Lawson & Penny Noble



Alan Garry & David Nickerson (for their enduring patience!)



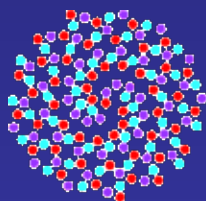
Alan Garry, Andrew Miller & Justin Marsh (tool development)



Randall Britten & Poul Nielsen



All the model authors who have provided advice and feedback



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